REMARKS

Amendments in the claims

The following claims are now pending in the present application following amendment herein: Claims 1–6 and 8–18. Four dependent claims (Claims 15–18) are added but the total number of claims remains not greater than 20. No excess claim fees are believed payable.

Claim 1 is amended without prejudice to focus the claim on an embodiment wherein the number of microreservoirs within the matrix is 10^3 to 10^9 per cm^2 of the surface of the matrix, and wherein the maximum diameter of the microreservoirs is not only less than the thickness of the matrix but is not greater than 35 μm. Support for the recited number of microreservoirs is found in the specification as filed at, for example, page 7, lines 10–12 (corresponding to paragraph **[0037]** of the application as published under US 2004/0081683). Support for a maximum diameter of microreservoirs not greater than 35 μm is found in the specification as filed at, for example, page 8, lines 26–28 (corresponding to paragraph **[0042]** of the application as published). Claim 1 is also amended to delete the phrase "and optionally at least one crystallization inhibitor"; this deletion is made to enhance clarity and will be seen to have no effect on scope of the claim as the previously recited component is optional.

Amendments to Claim 1 are made in the interest of maintaining conformity to claims in copending application Serial No. 10/623,864, of record in the present case, and are not necessitated by any ground of rejection in the present Action.

Claims 1, 2, 11 and 12 are amended to provide clearer antecedent basis.

Claim 7 is canceled without prejudice, it being Applicant's present intention to pursue the subject matter of this claim in copending application Serial No. 10/623,864.

New Claims 15 and 16, reciting crystallization inhibitors, find support in the specification as filed at least at page 13, lines 8–15, corresponding to paragraph **[0061]** of the application as published.

New Claim 17, reciting that the number of microreservoirs is 10^3 to 10^9 per cm^2, finds support in the specification as filed at least at page 7, lines 12–13 (corresponding to paragraph **[0037]** of the application as published).

New Claim 18, reciting that the maximum diameter of the microreservoirs is 2.5 to 30 μm, finds support in the specification as filed at least at page 8, lines 23–28 (corresponding to paragraph **[0042]** of the application as published), where an exemplary matrix thickness of 50 μm and a preferred maximum size of 5% to 60% of the thickness of the matrix (*i.e.*, 2.5 to 30 μm) are disclosed.

Opportunity has been taken, in amending the claims, to correct typographical errors, to rephrase where it has been desirable to do so for enhanced clarity, and to present subject matter where necessary in terms more in accordance with standard U.S. claim drafting practice.

No new matter is added, and no change in inventorship is believed to result from amendment of the claims as proposed herein.

RESPONSE TO OFFICE ACTION DATED AUGUST 10, 2007

1. Provisional double patenting rejection

The provisional rejection of Claims 1, 2, 5–7 and 10–14 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1–7 of copending application Serial No. 10/623,864 is maintained in the present office action.

The Action states that "Applicant will file a terminal disclaimer when allowable subject matter is indicated." It is respectfully noted that Applicant has not committed to filing a terminal disclaimer, but has indicated in the response dated March 5, 2007 that it may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the '864 application issues as a patent. Applicant maintains the right to overcome the present rejection by argument or by terminal disclaimer.

2. Rejection under 35 U.S.C. §103(a)

Claims 1–14 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 3,797,494 (Zaffaroni) in view of U.S. Patent No. 5,500,222 (Lee), U.S. Patent Application Publication No. 2004/0013620 (Klose), U.S. Patent No. 5,217,718 (Colley) and Goodman & Gilman's The Pharmacological Basis of Therapeutics (1990). This rejection is respectfully traversed.

No admission is made herein that any of the cited documents constitutes prior art to the present invention. It is again noted that Klose is not statutory prior art against the present invention, having published after the priority date of the present application. However, as brought to the Examiner's attention in Applicant's previous response dated March 5, 2007, Klose claims priority *inter alia* to U.S. Patent No. 6,299,900 (herein "Reed"), which provides at col. 5, line 7 – col. 9, line 46 an extensive laundry list of drugs said to be deliverable through skin. Included in this extensive list are "dopamine-2 agonists such as S(–)-2-(N-propyl-N-2-thienylethylamino)-5-hydroxytetralin (N-0923)" (col. 6, lines 12–13). In responding to the present rejection, Applicant substitutes Reed for Klose as in the previous response.

2.1. No teaching or suggestion of a selectively free-base permeable matrix

At the outset, it is respectfully pointed out that the statement in the present Action (page 7, lines 15–17) that "Applicant argues that Zaffaroni does not teach that the amine functional drug is in its free base form" is incorrect. That statement mischaracterizes Applicant's argument in its March 5, 2007 response regarding the selective permeability property recited in the present claims, specifically, that "Zaffaroni fails to disclose ... a matrix permeable to an amine functional drug in its free base form but impermeable to the drug in its protonated form." As a key part of Applicant's showing of non-obviousness has not been responded to in the present Action, re-assertion of the same ground of rejection as previously applied and the consequent finality of the present Action are in Applicant's view improper.

Applicant once again submits that Zaffaroni fails to disclose selection of an adhesive matrix that is (a) permeable to an amine functional drug in its free base form but (b) impermeable to the drug in its protonated form. None of the secondary references supplies this missing element, a critical feature of the present invention. Zaffaroni teaches, *inter alia*, that:

- "any of the well-known dermatologically acceptable pressure-sensitive adhesives can be used in practicing this [*i.e.*, Zaffaroni's] invention" (col. 14, lines 60–62, emphasis added);
- "the adhesive must be permeable to passage of the drug" (col. 15, lines 23–24);
- "simple pharmacologically acceptable derivatives of the drugs, such as ... salts ...

having the desired polymeric permeability or transport properties can be prepared and used in practicing the invention" (col. 13, lines 7–12).

Thus there is no recognition by Zaffaroni of the importance of satisfying all of the following conditions: (1) providing an amine-functional drug in its free base form; (2) selecting an adhesive that is permeable to passage of the drug in its free base form; and (3) selecting from among such adhesives an adhesive that is impermeable to the drug in its protonated form. Even if Zaffaroni, in his extensive laundry-lists of drugs (col. 12, lines 9–68) and, separately, of adhesives (col. 14, line 60 – col. 15, line 20), mentions specific amine-functional drugs and specific adhesives respectively, nowhere does Zaffaroni make any suggestion that would lead one of ordinary skill to partner an amine-functional drug in free base form with an adhesive that is selectively free-base permeable, *i.e.*, simultaneously permeable to the free base form and impermeable to the salt (protonated) form of the same drug. And again, none of the secondary references supplies the missing suggestion.

To further clarify the point made immediately above, if (conservatively) Zaffaroni discloses about 90 drugs and about 290 adhesives, this represents over 26,000 possible drug-adhesive combinations. Only if armed with the insight, provided for the first time by the present disclosure (and not by any of the secondary references), that a particularly useful combination is an amine-functional drug in free base form and a selectively free-base permeable adhesive, could one of ordinary skill in the art select from over 26,000 options to arrive at the present invention.

That insight is clearly set out in the present specification, for example at page 2, lines 29–31, referring to the importance of "preventing back diffusion of the drug portion which is ionized in the skin according to its pKa value from the skin tissue into the TDS." In other words, a selectively free-base permeable adhesive is effective to provide one-way transfer of an amine-functional drug from the TDS to the skin because in the skin, or at the skin-TDS interface, the drug tends to become protonated and cannot back-diffuse to the microreservoirs in the TDS.

Several of the findings of the present inventors set forth as Examples in the present specification reinforce this point. See in particular Example 3, especially the comparison of

in vitro skin permeation profile for a TDS of the invention, in which the drug is present in free-base form and the adhesive system is selectively free-base permeable, with that for a comparative TDS, in which the drug is present in protonated form and the adhesive system is permeable to such protonated form. The results of this comparison are shown graphically in Fig. 7, which clearly shows greatly enhanced skin permeation when a selectively free-base permeable adhesive system is used.

2.2. No teaching or suggestion of microreservoirs of diameter 35 μm or smaller

Applicant believes that the showing above, relating to importance of a selectively free-base permeable adhesive system, is sufficient to overcome the present ground of rejection. However, at least one additional distinction over the present combination of references relates to the size and number of microreservoirs. It will be understood that size and number are to some extent interrelated inversely.

As amended herein, Claim 1 recites that the matrix contains 10^3 to 10^9 microreservoirs per cm^2 of the surface of the matrix, and that the maximum diameter of the microreservoirs is less than the thickness of the matrix, and not greater than 35 μm. Teaching or suggestion of either of these features is not found in Zaffaroni, and none of the secondary references supplies the missing features. Zaffaroni states that microcapsules prepared by coacervation (which differ from the present microreservoirs in having a capsule shell or coating) "have an average particle size of from several tenths of a micron to 5,000 microns" and adds that "this feature is not critical to the practice of the invention" (col. 10, lines 34–37, emphasis added). Zaffaroni also states that "[u]sually, the micro-capsules have an average particle size of [from] 1 to 1000 microns, although this is not critical to the invention" (col. 10, lines 62–64, emphasis added). Further, Zaffaroni discloses that the adhesive layer can be 0.01 to 7 mm (*i.e.*, 100 to 7000 μm) thick (col. 11, lines 1–2). Thus, Zaffaroni fails to recognize the importance of microreservoirs that are smaller in maximum diameter than the thickness of the adhesive matrix, and in particular that are no larger than 35 μm in diameter. Again, this deficiency of Zaffaroni is not corrected by any of the secondary references.

It could not have been predicted by one of ordinary skill in the art at the time of the present invention, reading Zaffaroni in view of the secondary references, that, if an amine-

functional drug in free base form were partnered with a selectively free-base permeable adhesive system (such partnering being itself non-obvious as shown above), it would be important to ensure a maximum microreservoir diameter less than the thickness of the matrix, and no larger than 35 μm. Not until the present invention was it recognized that substantial direct exposure of microreservoirs to the skin surface (which would be the result of excessively large microreservoirs) would permit significant back diffusion from the skin to the TDS through by-passing the adhesive barrier to permeation of the protonated drug. See, for example, the present specification at page 9, lines 1–11, stating:

> As the maximum diameter of the microreservoirs in the direction of the cross-section of the matrix, *i.e.* between the release surface and the backing layer, is less than the thickness of the matrix, direct contact between the skin and the basic microreservoirs containing the amine-functional drug is avoided, if not at all prevented. Owing to the slightly acidic pH of the skin, direct contact between the skin and the microreservoirs in the matrix leads to protonation of the amine-functional drug, thereby deteriorating the semi-permeability of the matrix.

Adjustment of microreservoir number and diameter are therefore not simple matters of "optimization" of a TDS for an amine-functional drug, but (contrary to the express teaching of Zaffaroni) are critical to success.

2.3. Rejection under 35 U.S.C. §103(a): general remarks

As demonstrated above, not all limitations of Claim 1 are taught or suggested by Zaffaroni in view of Lee, Klose (Reed), Colley and Goodman & Gilman's. For at least this reason, the present Action fails to make a *prima facie* case of obviousness of Claim 1 over the cited combination of references. Notwithstanding the Examiner's remarks with respect to other claims, these claims each embody all the limitations of Claim 1 from which they depend or which they reference, and are therefore nonobvious at least for the same reasons that Claim 1 is nonobvious. If an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. MPEP 2143.03.

Applicant respectfully requests withdrawal of the present rejection under 35 U.S.C. §103(a).

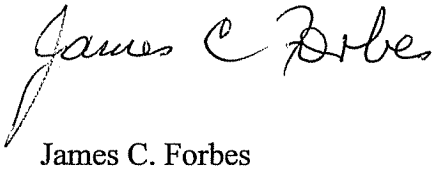
3. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.

Respectfully submitted,

HARNESS, DICKEY & PIERCE, P.L.C.



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